GEBELİKTE PROGESTERON KULLANIMI

(Progesterone use in Pregnancy)

Doç. Dr. Eray Çalışkan

Definition and Epidemiology: Preterm birth

- Delivery between 20 th wks of gestation until 37 wks of gestation

- 7-12% of all pregnancies

- In Turkey 125.000 /year
- %11.97
- 56 th in the world

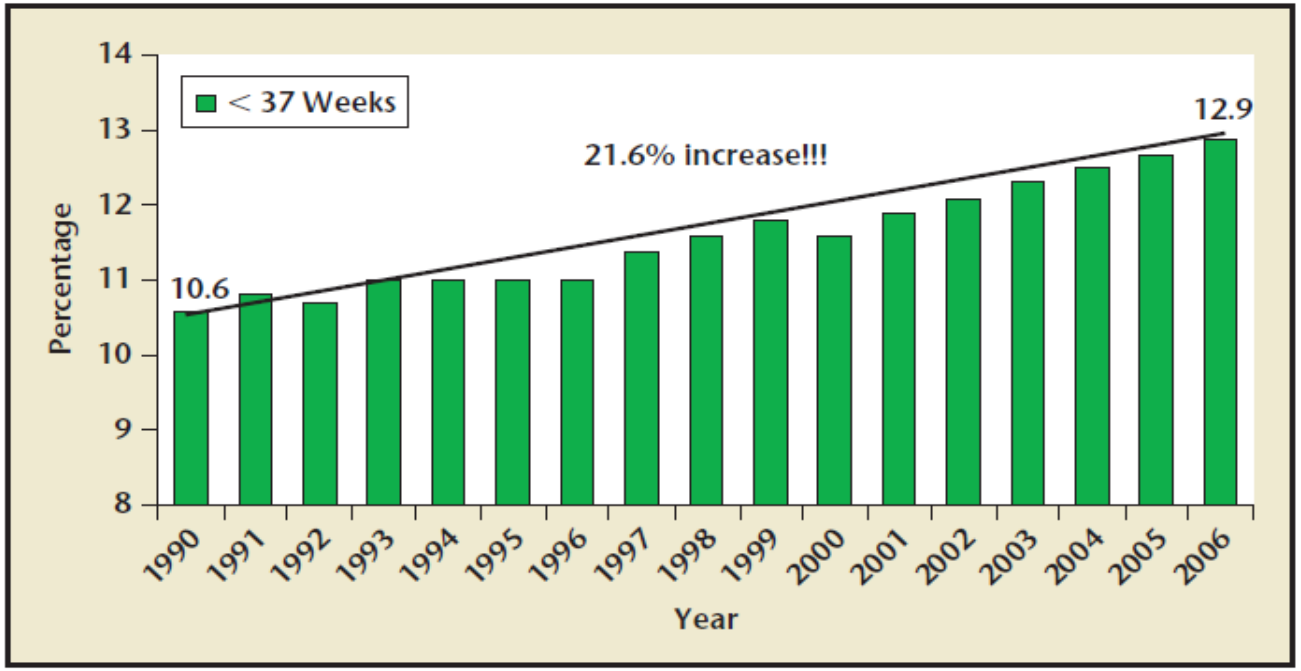


Figure 1. *Trends in the preterm birth rate in the United States.*

Preterm birth rate according to gestational age

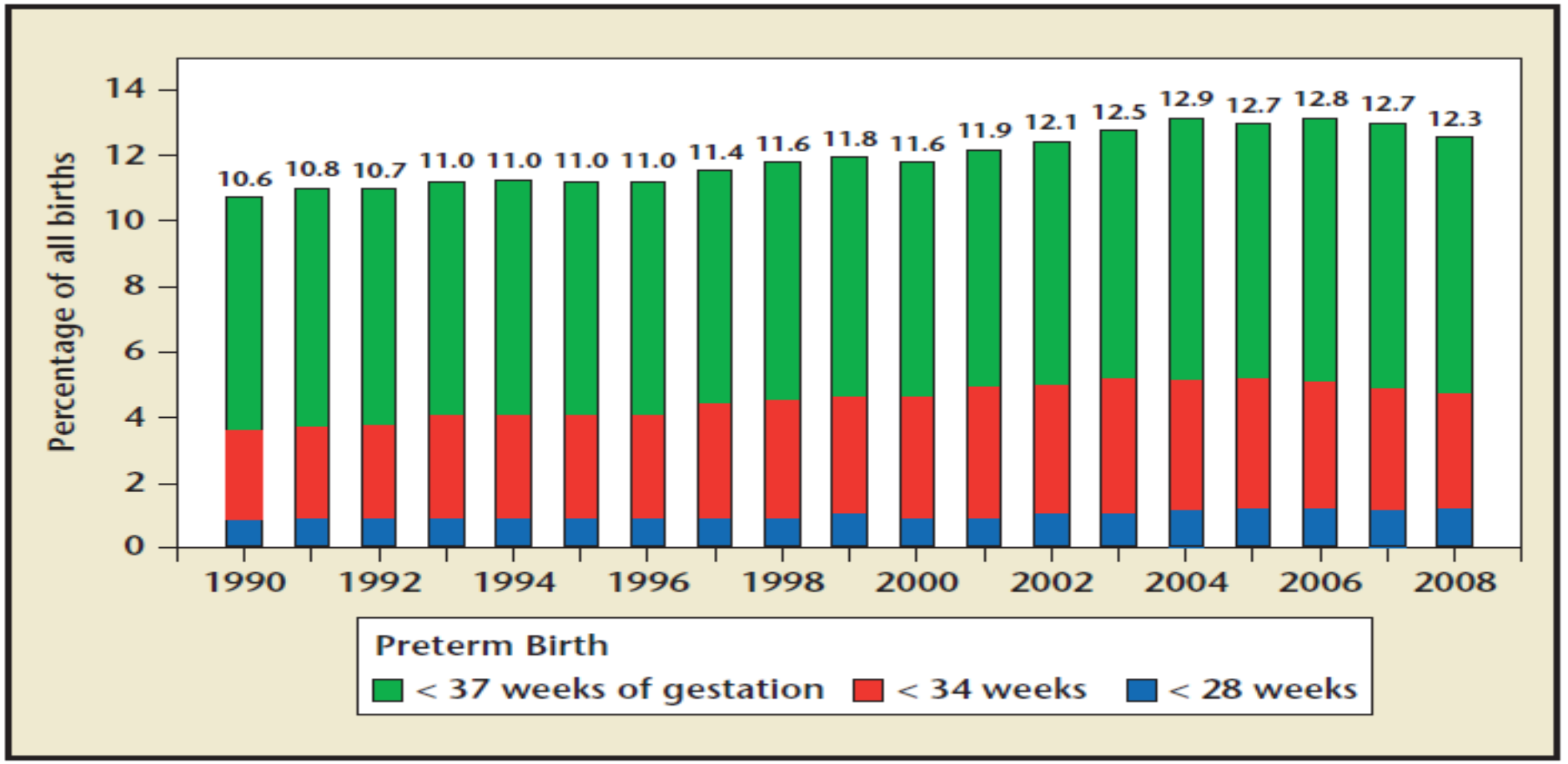


Figure 1. *Incidence of preterm birth in the United States, 1990-2008. The incidence of preterm birth in the United States is shown, including overall preterm birth (< 37 weeks of gestation), < 34 weeks of gestation, and < 28 weeks of gestation. Data are from the CDC/National Center for Health Statistics (http://www.cdc.gov/nchs/; accessed February 18, 2011).*

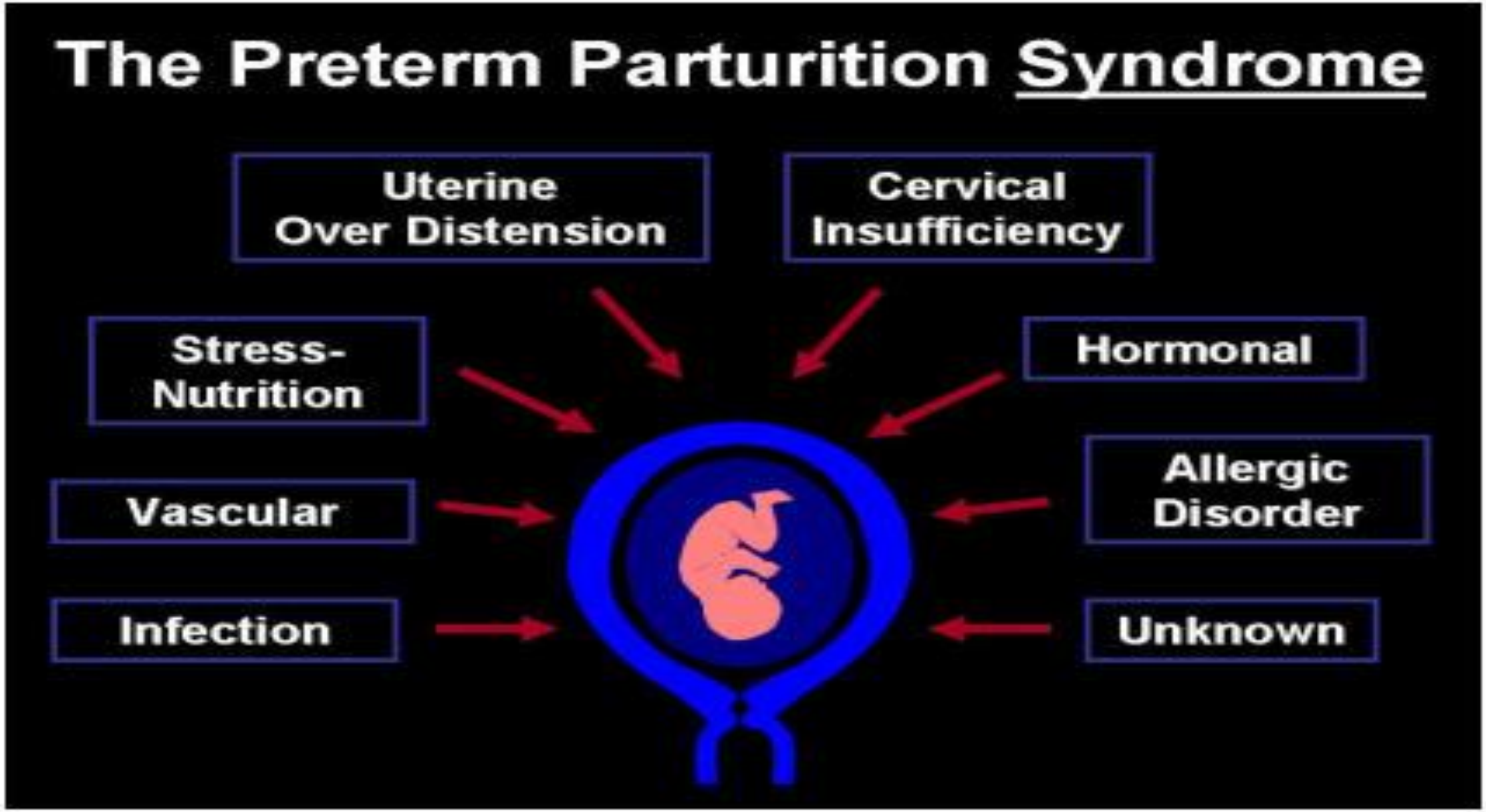
Norwitz ER et al., 2011

[Rev Obstet Gynecol. *2011;4(2):60-72*

Multifactorial Problem

Table 1. Commonly recognized etiologies and pathways leading to spontaneous preterm birth

Pathway	Examples	Mechanistic Effectors	Gestational Age When Predominant
Infection or Inflammation	Intrauterine Lower genital tract Systemic	Pro-inflammatory cytokine/ prostaglandin cascade Matrix metalloproteinases	Early preterm birth (24-32 weeks)
Decidual Hemorrhage	Thrombophilias, Placental abruption Autoantibody syndromes	Thrombin Matrix metalloproteinases	Early or late preterm birth
Maternal/Fetal HPA Activation	Stress	Maternal/Fetal HPA activation Placental CRH Estrogens Immune modulation	Late preterm birth (32-36 weeks)
Pathologic Uterine Overdistension	Multifetal gestation Polyhydramnios	Expression of gap junctions proteins Prostaglandins Oxytocin receptors	Late preterm birth


The Preterm Parturition Syndrome
Uterine Over Distension
Cervical Insufficiency
Stress-Nutrition
Hormonal
Vascular
Allergic Disorder
Infection
Unknown

PRIMARY PREVENTION

- Improve general maternal health
- Avoid risk factors
- Quit smoking
- Avoid BMI <18 or >35
- Avoid stress
- Prevent frequent pregnancies

Cochrane meta-analysis of 17 articles (2013)

Protection from preterm birth

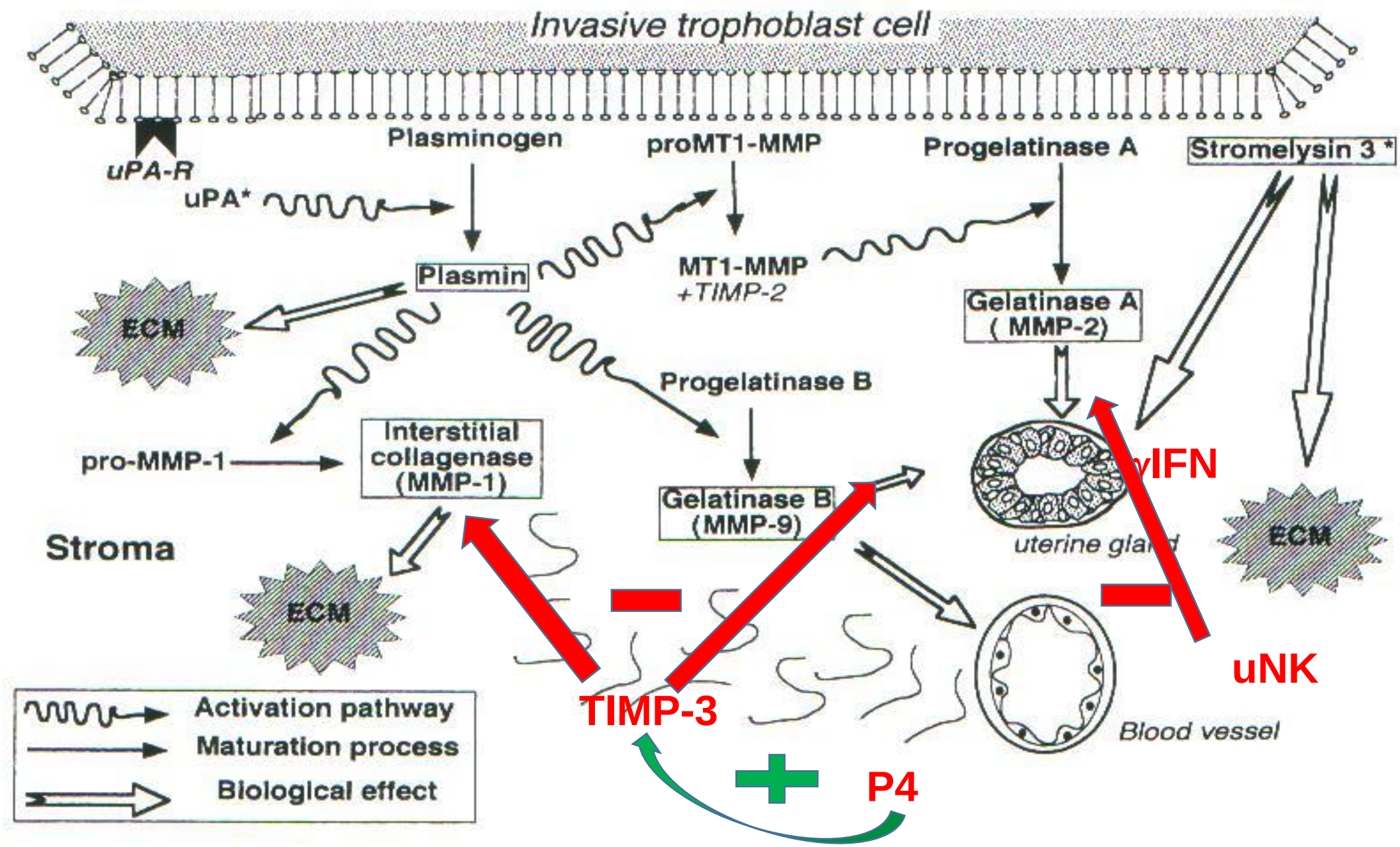
- 9.59 % to 9·07 %

- Quiting smoking (decrease by 0.01)
- Single embryo transfer (0.06)
- Cerclage (0.15)
- Progesterone (0.01)
- Preventing iatrogenic deliveries (0.29).

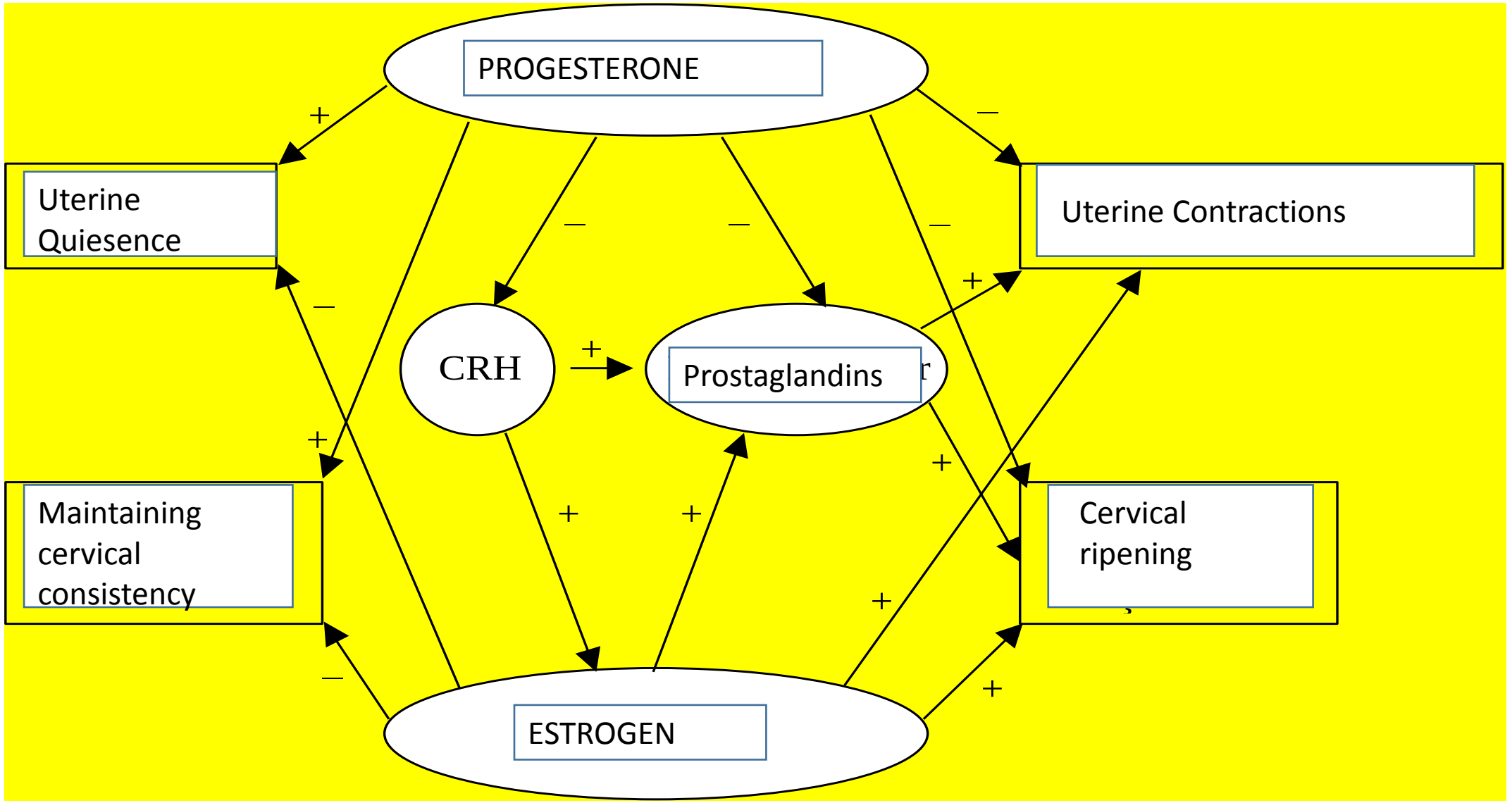
Chang, 2012, Lancet. Preterm prevention analysis group

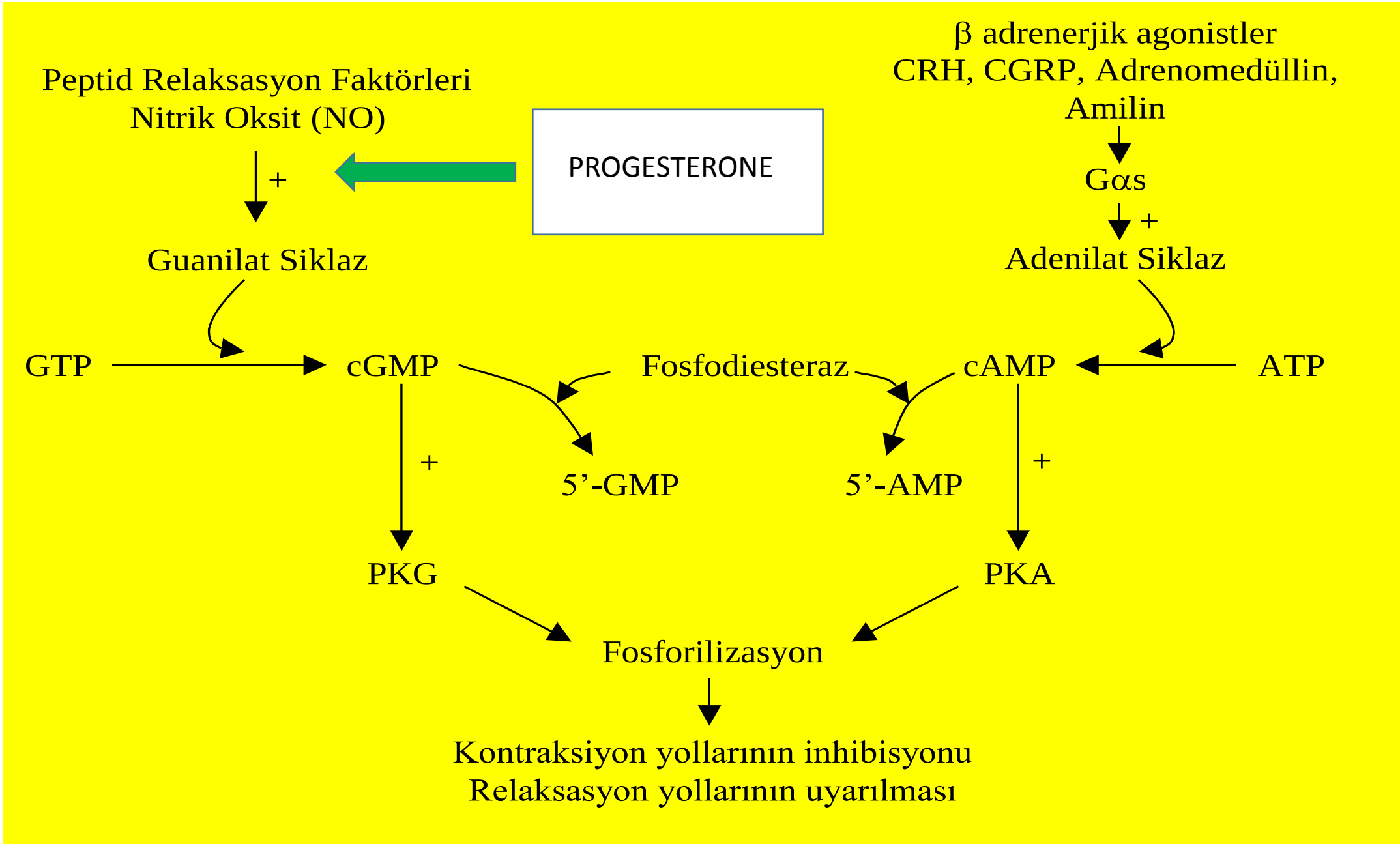
Progesterone mechanism of action

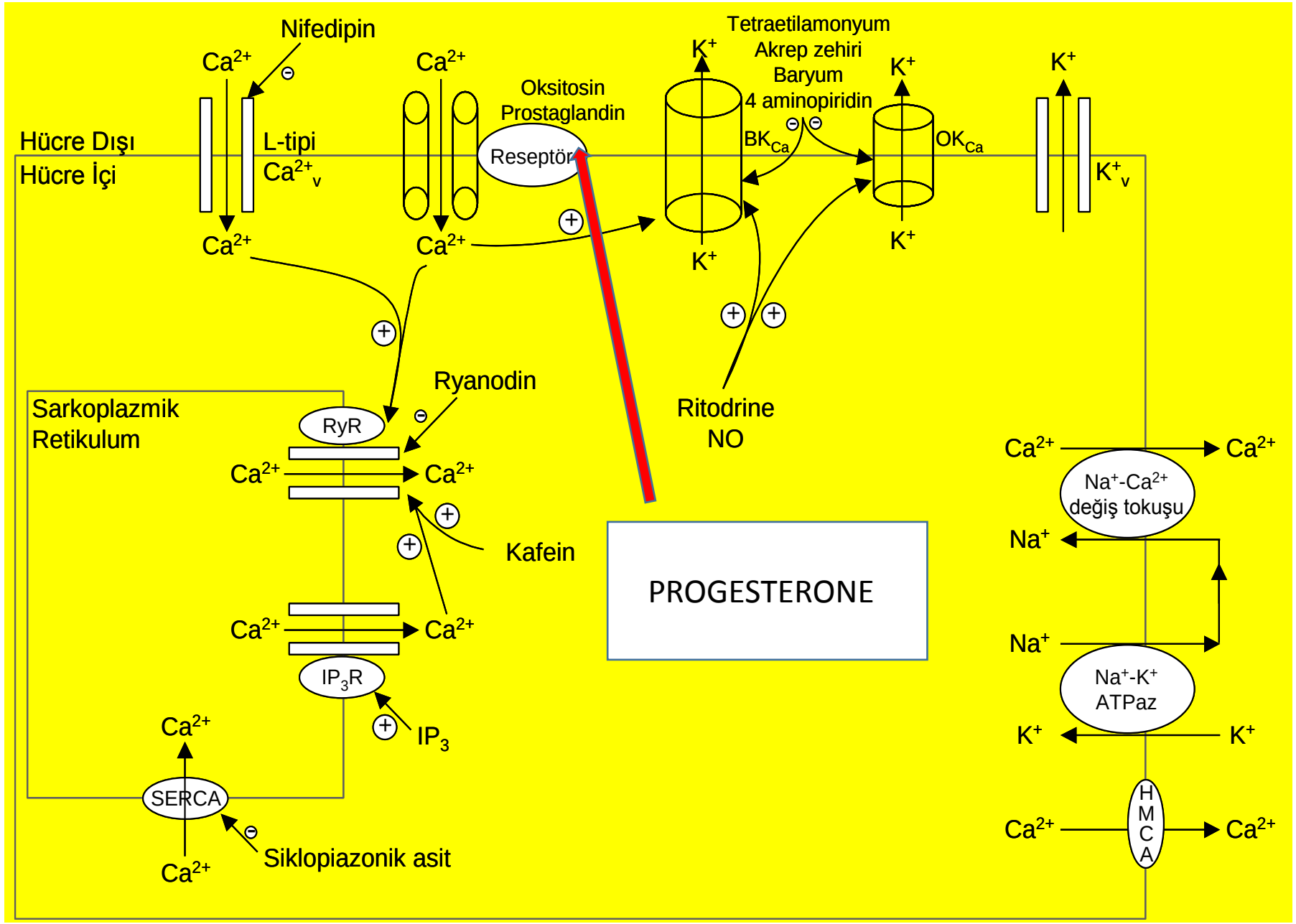
- The mechanism of action is not well known
- Blocks PgF2α ve α-adrenerjik receptors
- Decrease oxytocin receptors in the uterus
- Upregulates nitric oxide
- Blocks intracellular gap junctions



TGF-β inhibit MMP production


PROGESTERONE
Uterine Quiesence
Uterine Contractions
CRH
Prostaglandins
Maintaining cervical consistency
Cervical ripening
ESTROGEN


Peptid Relaksasyon Faktörleri
Nitrik Oksit (NO)
+
PROGESTERONE
β adrenerjik agonistler
CRH, CGRP, Adrenomedüllin,
Amilin
Gαs
+
Guanilat Siklaz
Adenilat Siklaz
GTP
cGMP
Fosfodiesteraz
cAMP
ATP
+
5'-GMP
5'-AMP
+
PKG
PKA
Fosforilizasyon
Kontraksiyon yollarının inhibisyonu
Relaksasyon yollarının uyarılması


Nifedipin
Ca2+
L-tipi
Ca2+v
Hücre Dışı
Hücre İçi
Oksitosin
Prostaglandin
Reseptör
Tetraetilamonyum
Akrep zehiri
Baryum
4 aminopiridin
K+
BKCa
OKCa
K+v
Ryanodin
RyR
Sarkoplazmik
Retikulum
Kafein
IP3R
IP3
SERCA
Siklopiazonik asit
Ritodrine
NO
PROGESTERONE
Na+-Ca2+
değiş tokuşu
Na+
Na+-K+
ATPaz
HMCA

Indirect evidence for Progesterone

- Progesterone receptor blocker Mifepristone

- Induce abortion
- Induce labor contractions
- Cause cervical ripening

Progesterones used in pregnancy

TABLE 3
Progesterone: pharmacologic types and protocols

Type	Route	Dose (mg)	Timing	References
Synthetic 17P	IM	250	Weekly from 16–20 wk	7,12,15,19
	IM	341	Twice weekly	11,19
	IM	250	Thrice weekly	19
	IM	500	Weekly	15
	IM	250	Every 3 days from 28 wk	15
	IM	1000	Weekly from 16 wk	15
	IM	25	Every 5 days	14
Natural progesterone	Vaginal	200	Nightly, 24–33 wk	8,19
	Vaginal	400	Daily, 18 wk to delivery	6,19
	Vaginal	100	Daily capsules to 34 wk	13
	Vaginal	90	Daily, 18 wk to delivery	9
	Oral	900–1600	Daily, from onset of PTL	18

IM, intramuscular; *PTL*, preterm labor; *17P*, 17-alpha-hydroxyprogesterone.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

Synthetic PROGESTERONE : No teratological effect on genitalia or gender role

Preterm birth and progesterone

- Prevention
- History or examination based prevention
- Treatment / tocolysis
- Guidelines
- Cost

Prevention

- No history but assumed risk at index pregnancy
- Twins
- Triplets

Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis

Jane E Norman, Fiona Mackenzie, Philip Owen, Helen Mactier, Kevin Hanretty, Sarah Cooper, Andrew Calder, Gary Mires, Peter Danielian, Stephen St... n Norrie

Vaginal progesterone gel in twin pregnancies between 24-34 wks: delivery bfr 34 weeks

	Progesterone		Placebo		Odds ratio progesterone vs placebo (95% CI)	p value
	n	Event (%)	n	Event (%)		
All pregnancies	247	61 (24·7%)	247	48 (19·4%)	1·36 (0·89–2·09)	0·16*
Monochorionic pregnancies	46	10 (21·7%)	45	14 (31·1%)	0·62 (0·24–1·58)	..
Dichorionic pregnancies	201	51 (25·4%)	202	34 (16·8%)	1·73 (1·06–2·83)	..

*Refers to p value for proportion in progesterone versus placebo group (from a logistic regression model adjusting for chorionicity). For test of interaction between monochorionic and dichorionic pregnancies, p=0·056.

Table 2: **Primary outcome (proportion of women delivering or with intrauterine death before 34 weeks) overall and by subgroup of chorionicity**

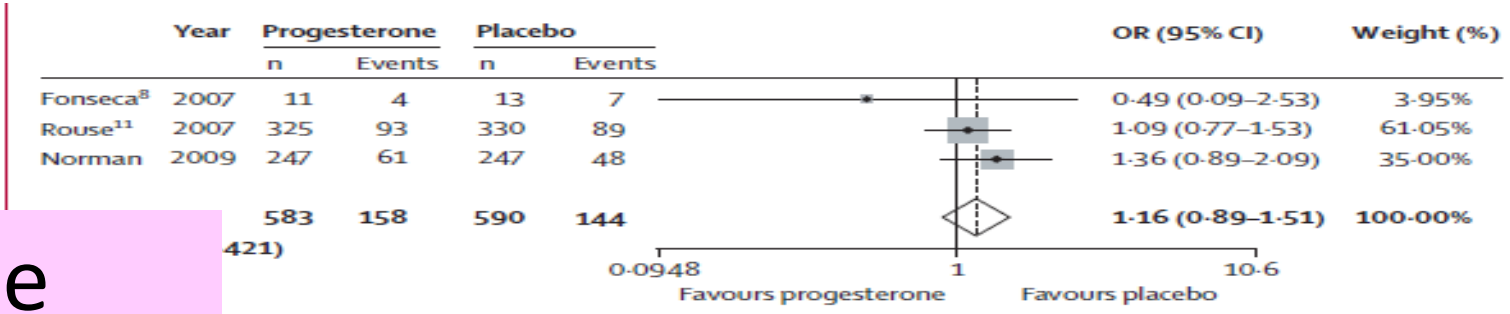


Figure 2: **Meta-analysis of the effect of progesterone in prevention of preterm delivery before 34 weeks' duration**

GDM
Progest: %12.9
Control: %4.0
p<0.001

No difference

Lancet 2009; 373: 2034–40

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N ENGL J MED 357;5 WWW.NEJM.ORG AUGUST 2, 2007

A Trial of 17 Alpha-Hydroxyprogesterone Caproate to Prevent Prematurity in Twins

Dwight J. Rouse, M.D., Steve N. Caritis, M.D., Alan M. Peaceman, M.D., Anthony Sciscione, D.O., Elizabeth A. Thom, Ph.D., Catherine Y. Spong, M.D., Michael Varner, M.D., Fergal Malone, M.D., Jay D. Iams, M.D., Brian M. Mercer, M.D., John Thorp, M.D., Yoram Sorokin, M.D., Marshall Carpenter, M.D., Julie Lo, M.D., Susan Ramin, M.D., Margaret Harper, M.D., and Garland Anderson, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

655 twin pregnancies
Weekly 17 OH Progesterone
From 16-20 until 35 hf

No difference

2011

Ultrasound Obstet Gynecol 2011; 38: 272–280
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.9093

Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone

L. RODE*†, K. KLEIN‡, K. H. NICOLAIDES§, E. KRAMPL-BETTELHEIM‡ and A. TABOR*† for the PREDICT Group

**Department of Fetal Medicine and Ultrasound 4002, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; †University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark; ‡Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria; §Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK*

Table 2 Maternal and twin pregnancy outcomes according to treatment group: progesterone ($n = 334$) or placebo ($n = 341$)

Outcome	*Progesterone group (n (%))*	*Placebo group (n (%))*	*Odds ratio (95% CI)*
Gestational age at delivery			
< 22 weeks	1/334 (0.3)	1/341 (0.3)	1.0 (0.1–16.4)
< 28 weeks	9/334 (2.7)	7/341 (2.1)	1.3 (0.5–3.6)
< 32 weeks	24/334 (7.2)	31/341 (9.1)	0.8 (0.4–1.3)
< 34 weeks	51/334 (15.3)	63/341 (18.5)	0.8 (0.5–1.2)
< 34 weeks, spontaneous delivery	42/334 (12.6)	53/341 (15.5)	0.8 (0.5–1.2)
< 34 weeks, induced delivery	9/334 (2.7)	10/341 (2.9)	1.0 (0.4–2.3)
< 37 weeks	158/334 (47.3)	179/341 (52.5)	0.8 (0.6–1.1)

675 twin pregnancies
Vaginal progesterone 200 mg
From 20-24 wks until 34 wks

No difference

Prevention of Preterm Birth in Triplets Using 17 Alpha-Hydroxyprogesterone Caproate

A Randomized Controlled Trial

*Steve N. Caritis, MD, Dwight J. Rouse, MD, Alan M. Peaceman, MD, Anthony Sciscione, MD, Valerija Momirova, MS, Catherine Y. Spong, MD, Jay D. Iams, MD, Ronald J. Wapner, MD, Michael Varner, MD, Marshall Carpenter, MD, Julie Lo, MD, John Thorp, MD, Brian M. Mercer, MD, Yoram Sorokin, MD, Margaret Harper, MD, Susan Ramin, MD, and Garland Anderson, MD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Maternal–Fetal Medicine Units Network (MFMU)**

OBJECTIVE: To assess whether 17 alpha-hydroxyprogesterone caproate reduces the rate of preterm birth in women carrying triplets.

intramuscular injections of either 250 mg of 17 alpha-hydroxyprogesterone caproate or matching placebo, starting at 16–20 weeks and ending at delivery or 35

Caritis SN et al., Obstet Gynecol, 2009 ; 113(2): 285–292

14 merkez
National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU)

134 triplet pregnancies
Weekly 17 OH Progesterone
From 16-20 until 35 hf

No difference

History or examination based prevention

- History of one preterm birth
- History of recurrent preterm births
- Short cervix at ultrasound

History of preterm birth in singletons: Progesterone vs placebo

- Start at 16-24 weeks: 250mg/wks 17-OH caproate or 100 mg intravaginal micronized progesterone: Preterm birth decrease by 30-50%
- 3-40% decrease in deliveries below 2500 g
- Mean increase in birth weight 475 g

TABLE 4
Selected perinatal outcomes among women with a history of spontaneous preterm birth: progesterone vs placebo

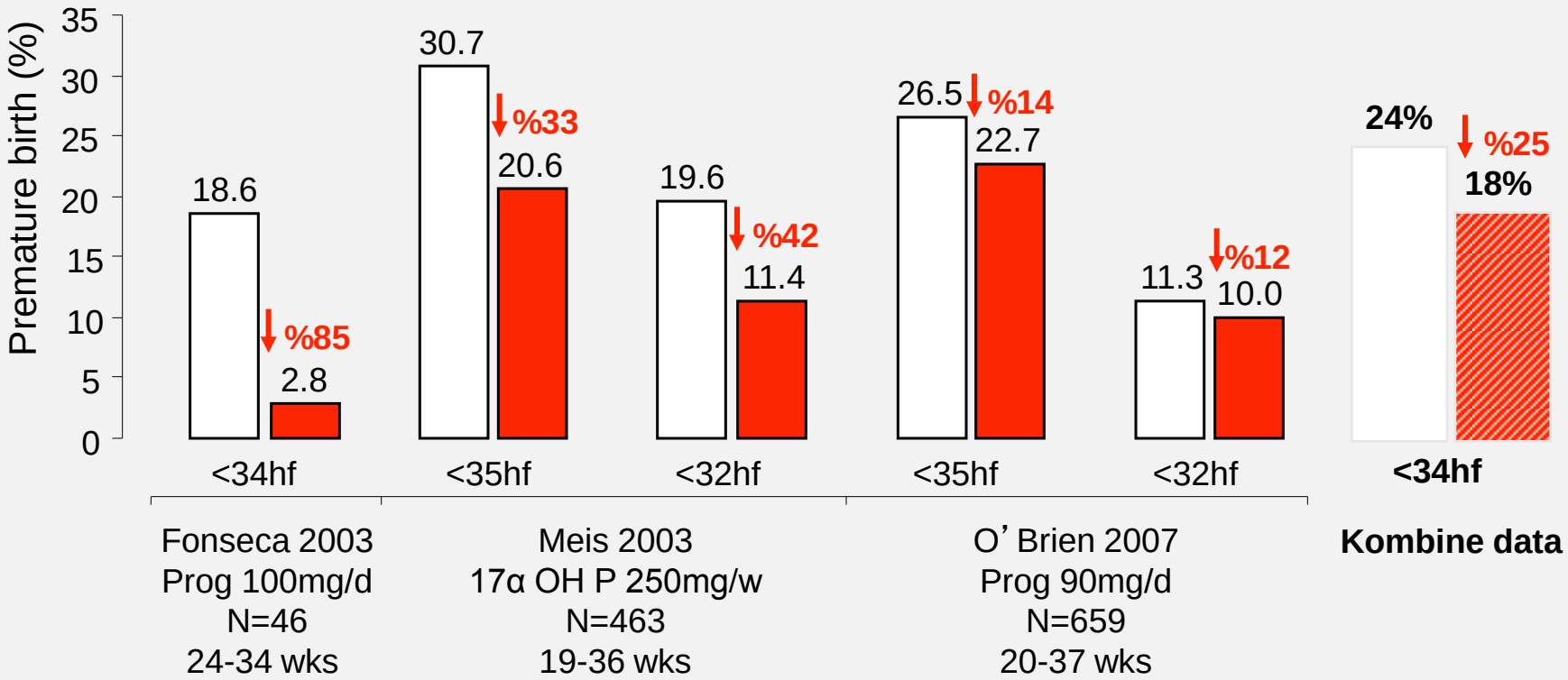
Study	PTB[a] wk: RR (95% CI)	Perinatal death RR (95% CI)	Neonatal death wk: RR (95% CI)	Mean GA (wk)[b]	RDS wk: RR (95% CI)
Dodd et al[19]	< 34: 0.15 (0.04-0.64)[c] < 37: 0.68 (0.45-1.02)	0.65 (0.38-1.11)	0.44 (0.16-1.18)	n/a	0.79 (0.57-1.10)
O'Brien et al[9]	≤ 32: 0.9 (0.52-1.56) < 37: 1.08 (0.76-1.52)	n/a	0.87 (0.29-2.60)	36.6 vs 36.6	0.91 (0.56-1.50)
Mackenzie et al[17]	< 37: 0.57 (0.36-0.90)[c]	0.39 (0.07-2.24)	n/a	+1.92 (0.37-4.21)[c]	0.64 (0.39-1.07)
Meis et al[12]	< 37: 0.66 (0.54-0.81)[c] < 32: 0.58 (0.37-0.94)[c]	0.64 (0.30-1.37)	0.44 (0.17-1.13)	n/a	0.63 (0.38-1.05)
da Fonseca et al[13]	< 37: 0.49 (0.25-0.96)[c]	n/a	n/a	n/a	n/a

CI, confidence interval; *GA*, gestational age; *n/a*, not available; *PTB*, preterm birth; *RDS*, respiratory distress syndrome.
Except where indicated, all data represent relative risks (95% CI) that, when < 1, favor progesterone.

[a] GA cut-off given; [b] Actual mean GA or difference in mean GA (95% confidence interval [CI]) for progesterone use compared with placebo or no treatment; [c] Results indicate statistical significance.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

Prophylactic progesterone in women with a history of preterm birth



Pregnant women with short cervix

If cervical length ≤15 mm intravaginal 200mg progesterone reduce birth before 34. weeks by 45-50 %

5 RCT meta-analysis: 775 women, 827 newborns

- <28 wks delivery (RR, 0.50; 95% CI, 0.30-0.81)
- <33 wks delivery (RR, 0.58; 95% CI, 0.42-0.80)
- <35 wks delivery (RR, 0.69; 95% CI, 0.55-0.88)

Romero R et al, AJOG, 2012

Pregnant women with short cervix

If cervical length ≤15 mm intravaginal 200mg progesterone reduce birth before 34. weeks by 45-50 %

5 RCT meta-analysis: 775 women, 827 newborns

- RDS — RR: 0.48; 95% CI, 0.30-0.76
- Composite neonatal morbidity and mortality — RR: 0.57; 95% CI, 0.40-0.81);
- Birthweight <1500 g — RR: 0.55; 95% CI, 0.38-0.80
- NICU admission — RR: 0.75; 95% CI, 0.59-0.94
- Mechanical ventilation — RR: 0.66; 95% CI, 0.44-0.98

Romero R et al, AJOG, 2012

Pregnant women with short cervix

- 10 country, 44 centers, 32091 women screened
- 458 pregnant women with cervical length 10-20mm intravaginal %8 90mg progesterone gel

Obstetric history (*n* (%))		
Nulliparous	125 (53)	126 (57)
No previous PTD*	204 (87)	195 (87)
≥ 1 previous PTD*	31 (13)	28 (13)

Hassan SS et al, Ultrasound Obstet Gynecol, 2011

Ultrasound Obstet Gynecol (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.9017

Vaginal progesterone reduces the rate of preterm bi in women with a sonographic short cervix: a multic randomized, double-blind, placebo-controlled trial

S. S. HASSAN[1,2], R. ROMERO[1,3,4], D. VIDYADHARI[5], S. FUSEY[6], J. K. BAXTER[7], M. P. S W. M. for

Preterm birth <28, 33, 35 wks
RDS
Composite morbidity/mortality
Birth weight< 1500 g

Different

Table 2 Gestational age at delivery and neonatal outcom allocated to receive vaginal progesterone gel ($n = 235$) co

Outcome	*Vaginal progesterone (n (%))*	*Placebo (n (%))*	*Relative risk (95% CI)*	P
Primary outcome				
Preterm birth < 33 weeks	21/235 (8.9)	36/223 (16.1)	0.55 (0.33–0.92)	0.020
Secondary outcomes				
Preterm birth < 28 weeks	12/235 (5.1)	23/223 (10.3)	0.50 (0.25–0.97)	0.036
Preterm birth < 35 weeks	34/235 (14.5)	52/223 (23.3)	0.62 (0.42–0.92)	0.016
Preterm birth < 37 weeks	71/235 (30.2)	76/223 (34.1)	0.89 (0.68–1.16)	0.376
Respiratory distress syndrome	7/235 (3.0)	17/223 (7.6)	0.39 (0.17–0.92)	0.026
Bronchopulmonary dysplasia	4/235 (1.7)	5/223 (2.2)	0.76 (0.21–2.79)	0.678
Proven sepsis	7/235 (3.0)	6/223 (2.7)	1.11 (0.38–3.24)	0.853
Necrotizing enterocolitis	5/235 (2.1)	4/223 (1.8)	1.19 (0.32–4.36)	0.797
Intraventricular hemorrhage, Grade III/IV	0/235 (0.0)	1/223 (0.5)	0.32 (0.01–7.73)*	0.305
Periventricular leukomalacia	0/235 (0.0)	0/223 (0.0)	Not estimable	NA
Perinatal death	8/235 (3.4)	11/223 (4.9)	0.69 (0.28–1.68)	0.413
Fetal death	5/235 (2.1)	6/223 (2.7)	0.79 (0.25–2.57)	0.700
Neonatal death	3/235 (1.3)	5/223 (2.2)	0.57 (0.14–2.35)	0.431
Composite outcome scores				
Any morbidity/mortality event	18/235 (7.7)	30/223 (13.5)	0.57 (0.33–0.99)	0.043
0–4 without NICU†				0.048
0–4 with NICU†				0.068
0–6 without NICU†				0.048
Birth weight < 2500 g	60/234 (25.6)	68/220 (30.9)	0.83 (0.62–1.11)	0.213
Birth weight < 1500 g	15/234 (6.4)	30/220 (13.6)	0.47 (0.26–0.85)	0.010

Unadjusted relative risk (RR) and 95% CI calculated using the Cochran–Mantel–Haenszel (CMH) test. *Based on Logit estimator with continuity correction. †Frequency of perinatal mortality/neonatal morbidity composite scores are provided in Appendix S4 online. NA, not applicable; NICU, neonatal intensive care unit.

17P IN PREGNANT WOMEN WITH SHORT CERVIX

Grobman (2012)

- 657 nulliparous, singleton pregnant women
- Cervix <30mm
- 16 > 36 weeks
- 17P 250mg IM/weeks vs placebo

- Incidence of preterm delivery < 35 wks SAME (13.5% vs 16.1%, p=0.35)
- Incidence of preterm delivery < 37 wks SAME (25.1% vs 24.2%, p=0.80)

Treatment

- In adjunct to tocolysis

Progesterone after threatened preterm labor

TABLE 5
Outcomes for progesterone vs placebo among other groups at risk for preterm birth

Study/indication	PTB[a] wk: RR (95% CI)	Mean GA (wk)[b]	Perinatal death wk: RR (95% CI)	Neonatal death wk: RR (95% CI)	RDS wk: RR (95% CI)
SHORT CERVIX					
Fonseca et al[8]	< 34: 0.56 (0.36-0.86)[c]		0.38 (0.10-1.38)	0.29 (0.06-1.42)	0.59 (0.26-1.29)
DeFranco et al[10] (< 28 mm)	≤ 32: 0 vs 29.6%[c]	+1.7 (36.3 vs 34.6)	n/a	0 vs 3.7%	0.18 (0.02-1.31)
Dodd et al[19]	< 34: 0.58 (0.38-0.87)[c]	n/a	0.38 (0.10-1.40)	0.29 (0.06-1.37)	0.59 (0.29-1.19)
MULTIPLE					
Rouse et al[7]	< 35: 1.1 (0.9-1.4)	-0.3 (34.6 vs 34.9)	n/a	n/a	1.2 (0.8-1.6)
Dodd et al[16]	< 37: 1.62 (0.81-3.25)	n/a	1.95 (0.37-10.33)	n/a	n/a
Dodd et al[19]	< 37: 1.01 (0.92-1.12)		1.95 (0.37-10.33)	n/a	1.13 (0.86-1.47)
THREATENED PTB					
Borna and Sahabi[6]	n/a	+2 (36.7 vs 34.5)[c]	n/a	n/a	0.30 (0.11-0.83)[c]
Facchinetti et al[11]	< 37: 0.29 (0.12-0.69)[c]	n/a	n/a	n/a	n/a
Dodd et al[19]	< 37: 0.29 (0.12-0.69[c]	n/a	n/a	n/a	0.30 (0.11-0.83)[c]

17 OH P
Vaginal P

CI, confidence interval; *GA*, gestational age; *n/a*, not available; *PTB*, preterm birth; *RDS*, respiratory distress syndrome; *RR*, relative risk.
Except where indicated, all data represent relative risks (95% confidence interval) that, when < 1, favor progesterone.

[a] GA cut-off given; [b] Difference in mean GA (respective mean GA) for progesterone use compared with placebo or no treatment; [c] Results indicate statistical significance.

Tita. Progesterone for preterm birth prevention: an evolving intervention. Am J Obstet Gynecol 2009.

Progesterone after preterm labor

- After Atosiban treatment
- 200 mg vaginal progesterone vs control
- Time to delivery increase significantly 55 vs 38 days

Areia 2013

- 17P treatment slows cervical shortening

Fachinetti 2009

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth.

- 36 RCT, 8523 women and 12,515 infants
- Progesterone vs placebo for women with a past history of spontaneous preterm birth
- Perinatal mortality RR: 0.50
- Preterm birth less than 34 weeks RR 0.31
- Infant birthweight less than 2500 g RR 0.58
- Assisted ventilation RR 0.40
- NEC RR 0.30
- Neonatal death RR 0.45
- NICU RR 0.24
- Preterm birth less than 37 weeks RR 0.55

- No differential effects in terms of route of administration, time of commencing therapy and dose of progesterone were observed for the majority of outcomes examined.

Dodd et al, Cochrane Database Syst Rev, 2013

Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth.

- Progesterone vs placebo for women with a short cervix identified on ultrasound
- Preterm birth less than 34 weeks — RR 0.64
- Preterm birth at less than 28 weeks' gestation — RR 0.59
- Increased risk of urticaria — RR 5.03

- Progesterone versus no treatment/placebo for women following presentation with threatened preterm labour
- Infant birthweight less than 2500 g — RR 0.52

Dodd et al, Cochrane Database Syst Rev, 2013

Guidelines for Progesterone use

SMFM Clinical Guideline www.AJOG.org

Progesterone and preterm birth prevention: translating clinical trials data into clinical practice

Society for Maternal-Fetal Medicine Publications Committee, with the assistance of Vincenzo Berghella, MD

- Singleton pregnancies with asymptomatic short cervix (<20mm) before 24. wk without prior preterm birth
- Vaginal progesterone (90 mg gel veya 200 mg suppository) should be given as a treatment option
- Cerclage or 17 P is not adviced

SMFM Clinical Guideline www.AJOG.org

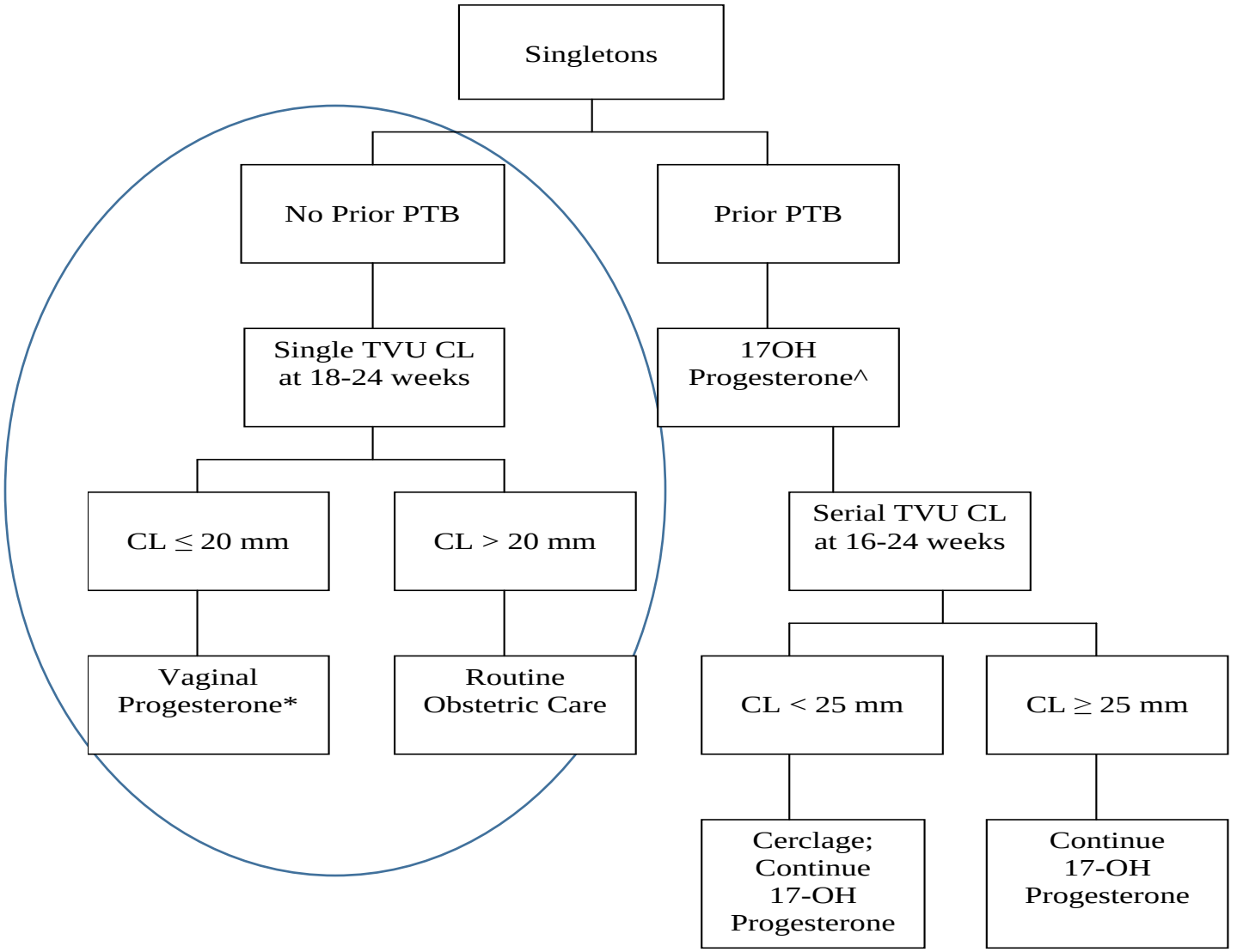
Progesterone and preterm birth prevention: translating clinical trials data into clinical practice

Society for Maternal-Fetal Medicine Publications Committee, with the assistance of Vincenzo Berghella, MD

- There is no data yet for advising universal cervical screening and vaginal progesterone treatment
- Universal screening is a viable option but not mandatory in the clinical routine
- No evidence of better outcome in multiple pregnancies

Society for Maternal-Fetal Medicine

Figure



ACOG, 2012

PTB, preterm birth; TVU, transvaginal ultrasound; CL, cervical length; ^250 mg IM every week from 16-20 weeks to 36 weeks; *e.g. daily 200 mg suppository or 90mg gel from time of diagnosis of short CL to 36 weeks

SMFM, AJOG May 2012

Preventing preterm delivery: CERCLAGE

- In women with recurrent preterm labor (and/or with short cervix), compared to no treatment cerclage , decrease the rate of preterm delivery without significantly decreasing perinatal mortality and neonatal morbidity

Perinatal deaths (8.4% vs 10.7%) ((RR) 0.78; 95% (CI) 0.61 to 1.00; 8 study, n:2391)
Neonatal morbidity (9.6% vs 10.2%) (RR 0.95; 95% CI 0.63 to 1.43; 4 study, n:818)
Preterm delivery (RR 0.80; 95% CI 0.69 to 0.95; 9 study, n:2898)
Maternal side effects (vaginal discharge, bleeding, fever (RR 2.25; 95% CI 0.89 to 5.69; 3 study, n:953).

Alferevic 2012 Cochrane

Women with prior preterm delivery: CERCLAGE

Meta-analysis (2011)

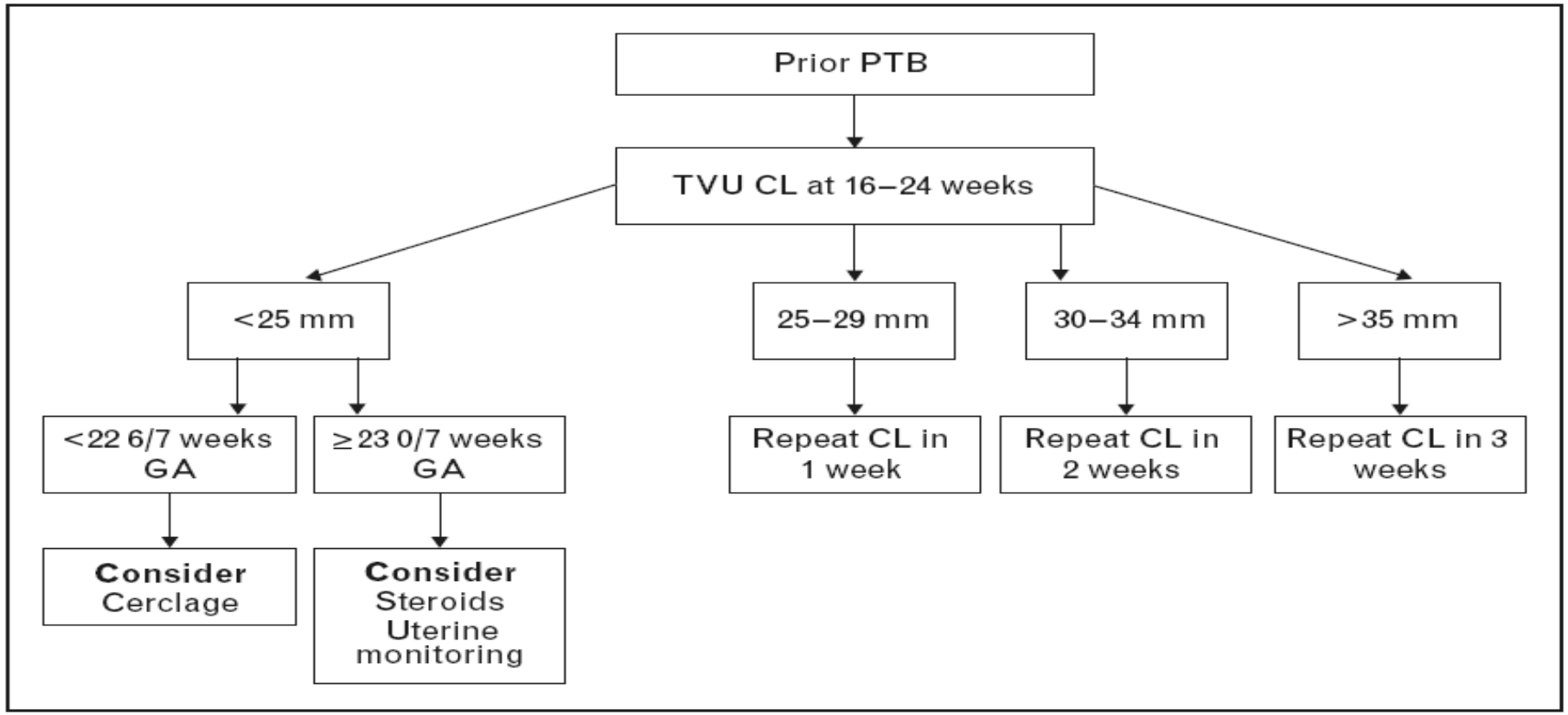
- Cervix (<25mm , <24 weeks)
- 5 randomized trial, 504 cases

- Preterm <35w (30%) decrease
- Cerclage has decreased preterm delivery in all gestational weeks
- < 37, 32, 28, and 24 wks

(Berghella 2011)

Women with prior preterm delivery: CERCLAGE

Figure 1 Algorithm for the assessment of cervical length (CL) by transvaginal ultrasound (TVU) in women with a prior preterm birth (PTB)

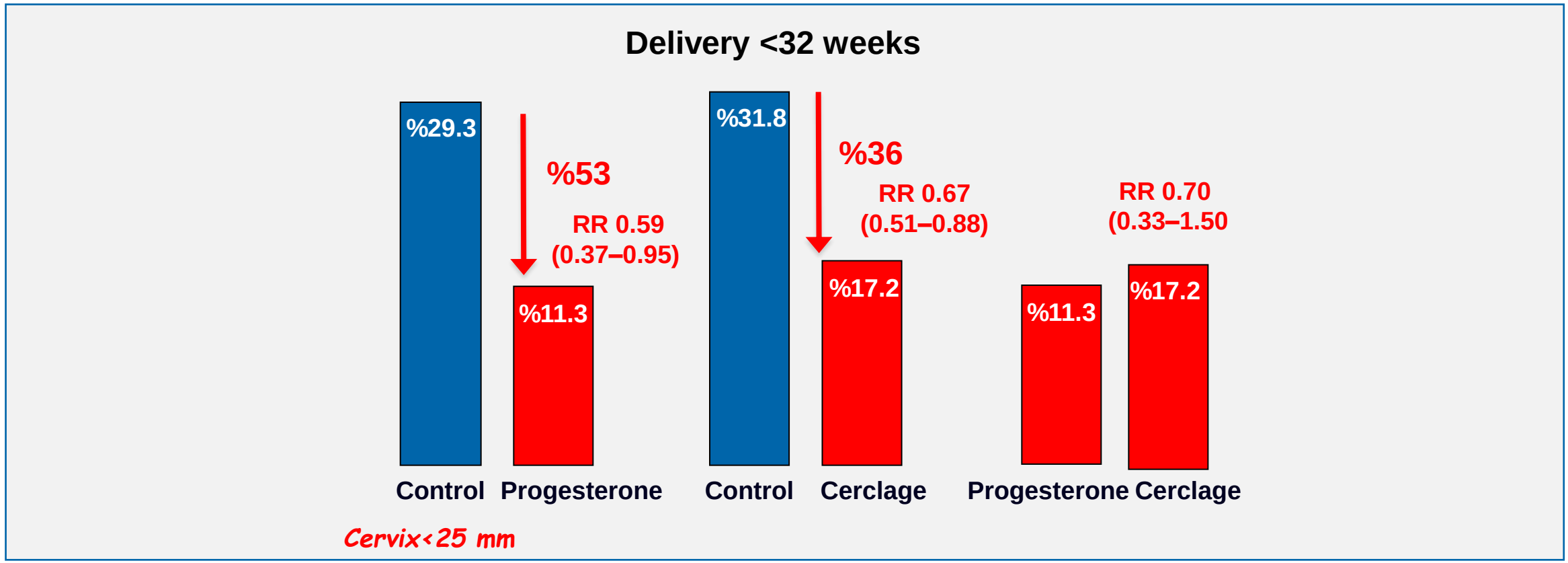


Grimens, J. Berghalk, V. Current Opionins. İn Obs. Gynecol 2007

PREVENTION OF PRETERM DELIVERY

4 trials vaginal progesterone / placebo, 5 trials cerclage ±
Capsul 200mg/g, suppository 100mg/g, gel 90mg/g
Vaginal progesterone and cerclage EQUALLY EFFECTIVE

CONCLUSION—Based on state-of-the-art methodology for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous preterm birth. The selection of the optimal treatment may depend upon adverse events, cost and patient/clinician preferences.



Conde-Agudelo A et al, metaanalysis, ACOG, 2013

NO PRIOR PRETERM DELIVERY BUT SHORT CERVIX: CERCLAGE?

Low risk group, cervix <25mm 16-24 weeks

- Cerclage HAS NOT DECREASED preterm delivery
- RR: 0.76; 95% CI, 0.52-1.15

Berghella 2005

Low risk group, cervix <15mm 22-24 weeks

- Cerclage HAS NOT DECREASED preterm delivery
- RR: 0.84; 95% CI, 0.54-1.31

To 2004

CONCLUSION

- Additional interventions such as tv-cervical length assessment should be performed for the diagnosis preterm delivery

- History based or short cervix based progesterone treatment is effective for the prevention of preterm delivery and improves neonatal outcomes

- Cerclage might be effective in patients with a history of prior preterm delivery and short cervix